attractive future problem to find out the origin of the difference in chemiluminescence properties of **2**, **7**, and **8**.

**Acknowledgment.** This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan.

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(6) Irradiations were carried out with a tungsten–bromine lamp through a Pyrex glass. The ratio of products **2**–**5** was not significantly altered by the use of a UV-cutoff filter ($K_2Cr_2O_7$ or $CuCl_2$–$CaCl_2$ solution) or by prolonged irradiation (up to 2 h).
(7) The dioxetanimine **2** and *tert*-butyl isocyanide (**5**) may be assumed to result from a perepoxide or zwitterion intermediate in analogy to the reaction of ketenes with singlet oxygen,[4] but we have now no clear evidence for it. To date, only a brief study was made for the reaction of ketenimines with singlet oxygen to give isocyanates and carbonyl fragments (Lee, K.-W., Ph.D. Dissertation, University of Southern California, 1975, pp 227–241). We have also found that various ketenimines give the corresponding carbonyl compounds and isocyanates, which will be described in a separate paper.
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(9) Chemiluminescence was measured by a Shimadzu RF-500 fluorescence spectrometer with a Hamamatsu R 446 photomultiplier tube. For quantitative chemiluminescence measurements, the sample solution of **2** ($\sim 10^{-2}$ M) was prepared by the photooxygenation of **1** in $CFCl_3$, using polymer-bound Rose Bengal instead of tetraphenylporphine as sensitizer, followed by filtration at −78 °C. To the solution of **2** thus prepared was added the equal volume of the stock solution of various concentrations ($10^{-4}$–$10^{-3}$ M) of each fluorescer in toluene, and the chemiluminescence was measured. Judging from the chemiluminescence decay and the NMR monitoring, the decomposition of **2** was not promoted by the fluorescers. The effect of the treatment of the solvents ($CFCl_3$ and toluene) with EDTA·2Na salt on the lifetime of **2** was also negligible.
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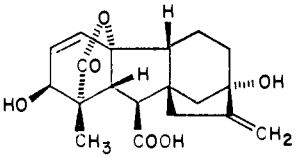
## Reductive Cyclization of Ethynyl Ketones in the Construction of a Significant Tricyclic Intermediate for the Synthesis of Gibberellic Acid

*Sir:*

The gibberellic acid structure **1**[1] has played a notable role in the generation of new reactions. The reductive cyclization



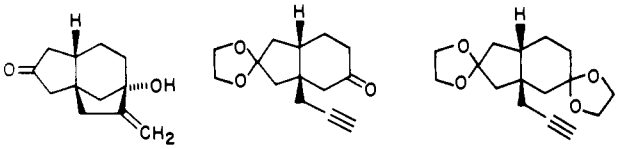
**1**

of 5-ethynyl ketones to methylenecyclopentanols[2] provides an excellent example (**2** → **3**). The reaction provides a direct

**2** **3**

approach to the methylenebicyclo[1.2.3]octanol system which is one of the most salient features of many of the gibberellins. We have therefore expended considerable effort to take advantage of the above cyclization and have used it in four different constructions of the tricyclic ketone **4**, the first synthesis of which we achieved almost 7 years ago.[3] We now outline three of the routes that we have followed to **4** and give the details of a fourth.

The central assumption on which these syntheses were based was that **4** should be reached readily via the cyclization of the ethynyl ketone **5**. The goal of our syntheses thus became its possible precursor, the diketal **6**. Scheme I illustrates one of



**4** **5** **6**

our early routes to **6**. We have described previously[4] the cyanohalo ketal cyclization of **7** to **8**,[5] mp 93–94 °C, and of **9** to **10**, mp 108–109 °C. The transformation of the angular cyano function into a propargyl group was carried out in the same manner in the hydrindan and decalin series. We describe it starting with the cyanohydrindan **8**. Reduction of the nitrile **8** (Dibal-H, toluene; hydrolysis with 5% acetic acid, 1 h at room temperature) gave the aldehyde **11**, mp 67–69 °C, which then led to the ethynylcarbinol **12**, mp 97–100 °C (lithium acetylide, THF–liquid $NH_3$; 50% overall yield from **8**). The desired net removal of the secondary hydroxyl group from **12** was then effected by formation of the mesylate (30% excess methanesulfonyl chloride–pyridine; 0 °C, 1 h; −20 °C, 48 h), followed by hydride reduction ($NaAl(OCH_2CH_2OCH_3)_2H_2$, toluene, −60 to −20 °C, 48 h) to the crude allene **13** which was then isomerized (lithium diisopropylamide, THF, −20 °C, 6 h) to the propargyl diketal **6** and finally hydrolyzed (1:7 20% hydrochloric acid–methanol, 2.5 h) to the nicely crystalline propargylindandione **14**, mp 107–108 °C (IR 2260, 1745, 1715 $cm^{-1}$). The decalindione analogue **15**, mp 118–120 °C, was produced by the same sequence of steps.[6]

Although these routes to the acetylenic diones **14** and **15** were successful, they were rather lengthy (the route to **14** from dihydroresorcinol via **8** took 14 steps), and they were not entirely stereospecific: the initial cis cyano diketals **8** and **10** were accompanied by ~5–8% trans isomers.

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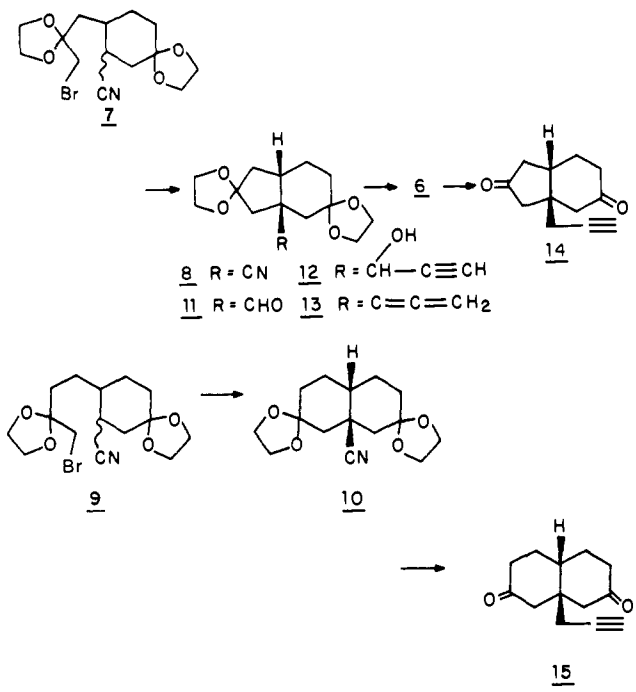
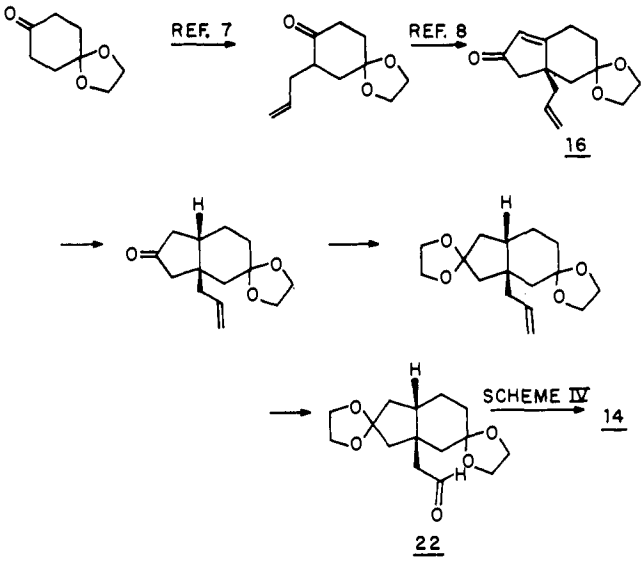
Scheme I




Scheme II

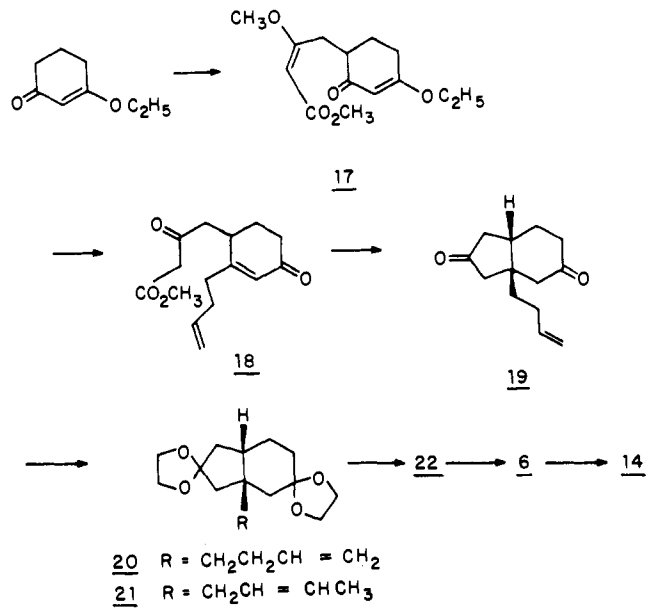



A somewhat shorter route to **14** (11 steps from 1,4-cyclohexanediol) was developed as sketched in Scheme II.

The process was quite effective (the overall yield of **14** from the indenone **16** was ~45%), but it was not entirely stereoselective because the $Li/NH_3$ reduction of **16** gave ~6% undesired trans isomer.

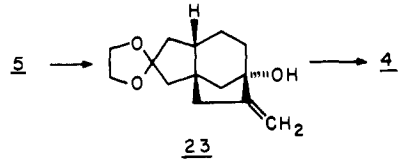
We therefore eventually developed yet another—entirely stereospecific—sequence which, like the cyanohydrindan route, takes advantage of the very versatile synthesis of 4-substituted 2-cyclohexenones which is now available[9] (Scheme III). The readily obtained **17** (mp 55–56 °C, 83% yield by alkylation of 3-ethoxycyclohexenone with methyl 3-methoxy-4-bromocrotonate) was treated with 3-butenylmagnesium bromide (THF, −78 °C) and hydrolyzed (1:4 30% perchloric acid–methylene chloride) to give **18** in ~50% yield. Intramolecular Michael addition[10] (sodium methoxide in methanol, room temperature), followed by decarbomethoxylation,[11] then gave, in ~45% yield, the *cis*-2,6-indandione **19**, bp 165 °C (0.4 mm). Transformation of **19** to the crystalline dione **14** was achieved in 35% overall yield by the following sequence: ke-

Scheme III




talization to give **20**, isomerization to **21** (4% potassium *tert*-butoxide in $Me_2SO$, 50 °C, 18 h, 85% yield); ozonolysis (methanol–THF–pyridine, −78 °C; followed by dimethyl sulfide cleavage) to the aldehyde **22** which was then converted into **6** by sequential treatment with chloromethylene triphenylphosphorane (from lithium butyl in THF, −30 °C) and lithium diisopropylamide (−25 °C, 1 h). Hydrolysis of **6** then again gave the propargyldione **14**, thus obtained in ~35% overall yield from the cis indandione **19**.

The crucial cyclization experiment to produce the tricyclic system **23** was performed on the monoketal **5**, easily obtained in 75% yield from **14** in the expected fashion (selective reduction of the cyclohexanone carbonyl with $NaBH_4$, ketalization, and oxidation with chromic acid–2-pyridine). The monoketal **5** (IR 1712 $cm^{-1}$) (6 g in 1 L of liquid $NH_3$ containing 150 mL of THF and 120 g of dry ammonium sulfate) was cyclized at reflux temperature, by addition of potassium metal (10 equiv) onto a perforated surface from which it was leached by the refluxing liquid ammonia. The process gave, in 60–70% yield, the tricyclic dioxolane **23** which underwent




acid hydrolysis (50% acetic acid) to octahydro-5-methylene-6-hydroxy-[3a$\beta$,6$\beta$,8a$\alpha$]-1*H*-3a,6-methanoazulen-2-one (**4**): mp 114–116 °C after crystallization from ether–pentane; IR 1745, 903 $cm^{-1}$; NMR $\delta$ 5.10 (t, 1 H), 5.25 (t, 1 H).

The structure of **4** was further confirmed unambiguously by an X-ray structure determination[12] which is discussed elsewhere, together with the direction of its kinetic enolization.

**Acknowledgment.** We thank the National Institutes of Health and the National Science Foundation for their support of this work.

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(3) The complete X-ray structure of our tricyclic ketone **4** has been in the literature since 1977,[12] and an outline of one of our more recent syntheses has been available (Taber, D. A. Diss. *Abstr.* **1975**, *35B*, 4399–4400. See also Danheiser, R. L. Ph.D. Thesis, Harvard, 1978). We were therefore surprised that the authors of a very recent communication outlining a synthesis of **23** and other derivatives of **4** (Corey, E. J.; Gorzynski Smith, J. *J. Am. Chem. Soc.* **1979**, *101*, 1038–1039) appeared unaware of our much earlier (and considerably shorter) synthesis.

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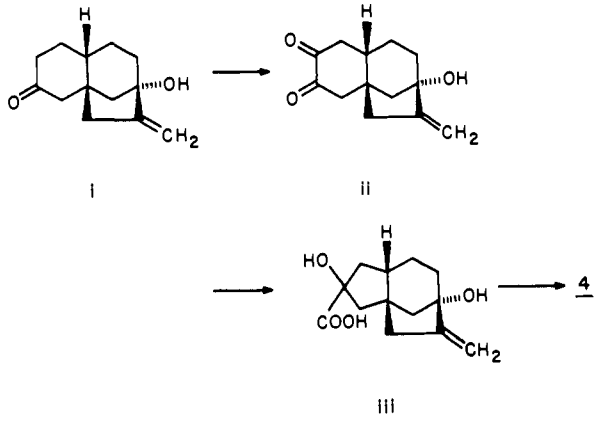
(5) The starting material **7** for the cyclization was made from 4-allylcyclohexenone (cf. ref 9) by (1) conjugate addition of cyanide (diethylaluminum cyanide) and dioxolane formation; (2) transformation of the allyl chain into the required $\alpha$-bromodioxolane by sequential formation of the bromohydrin (*N*-bromosuccinimide, dimethyl sulfoxide), the bromo ketone (chromic acid–acetone), and the bromo diketal. The overall yield from cyclohexane-1,3-dione to **7** was ~20%. It is a pleasure to acknowledge the important contributions of R. L. Danheiser to this particular sequence.

(6) Early and significant contributions to the synthesis of the acetylenic decalindione **15** were made by Dr. J. O. Gardner in this laboratory. This decalindione was our original intermediate to the tricyclic hydrindan **4.** This transformation was initiated by reductive cyclization (cf. **5** → **23**) to the tricyclic decalin derivative i. This was converted into the required hydrindan system by (a) oxidation ($O_2$, *tert*-butoxide) to the diketone ii; (b) benzilic rearrangement (2:3 20% KOH–propanol, reflux 24 h) to iii; (c) lithium



aluminum hydride reduction of the correspondlng methyl ester; and, finally, (d) perlodate cleavage to **4.**

(7) Stork, G.; Brizzolara, A., Jr; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

(8) Jacobson, R. M.; Raths, R. A.; McDonald, J. H., III *J. Org. Chem.* **1977**, *42*, 2545–2549.

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(10) Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978**, 2445–2448.

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(12) Harlow, R. L.; Simonsen, S. H. *Cryst. Struct. Commun.* **1977**, *6*, 689–693.

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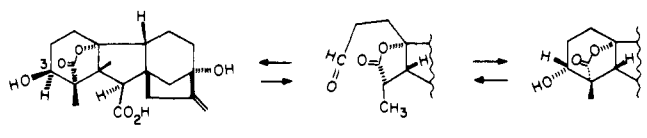
## An Unusually Simple Construction of Ring A of Gibberellic Acid

*Sir:*

It has been suggested[1] that the observed transformation[2] of dihydrogibberellic acid (**1**) into its (more stable) epimer **2** implies retroaldolization to the lactone aldehyde **3**. Its subsequent (reversible) reclosure would then result in the **1** → **2** equilibration.

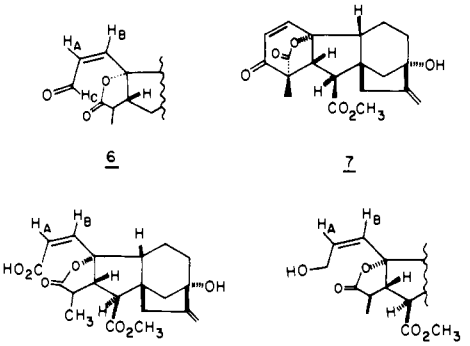


The implication that the dihydrogibberellic acid system might thus be synthesized via the open aldehyde **3** has, in fact, been the basis of some interesting model studies.[3]

The possibility of constructing the A ring area of gibberellic acid (**4**, R = H) *itself* (as opposed to much less strained models)[3] by such a process derives no support from the extensive chemistry of gibberellic acid. In contrast to its much more stable dihydro analogue **1**, gibberellic acid is isomerized, even with 0.01 N NaOH solution at room temperature, to isogibberellic acid[4] (cf. **4** → **5**).

The above result does not imply, however, that there might not be a *kinetic* path that would convert the open aldehyde **6** into gibberellic acid, a transformation which would simplify the problem of total synthesis to such an extent that it appeared worth trying, in spite of the poor prognosis.

The open aldehyde **6** was obtained from the well-known unsaturated ketone **7**,[5] starting with its cleavage (0.05 M



NaOH, 5 min at room temperature) to the unsaturated acid **8**:[6] mp 149–151 °C; 85% yield; NMR $\delta$ 5.76 ($H_A$, d, $J$ = 13 Hz), 6.03 ($H_B$, d, $J$ = 13 Hz).[7]

The acid was transformed into the desired aldehyde **6** by a three-step sequence: formation of the mixed anhydride (methyl chloroformate, triethylamine, THF, 15 min, room temperature; 90% yield); reduction (sodium borohydride, THF, 0 °C, 30 min) to the allylic alcohol **9** (mp 145–146 °C; 80% yield; NMR $\delta$ 5.42 ($H_B$, d, $J$ = 12 Hz), 5.75 ($H_A$, dd, $J$ = 5, 12 Hz)); oxidation ($MnO_2$ in methylene chloride, 12 h at room temperature) to the desired cis unsaturated aldehyde **6** (mp 122–123 °C; 77% yield; NMR $\delta$ 6.02 ($H_A$, dd, $J$ = 7, 13 Hz), 6.43 ($H_B$, d, $J$ = 13 Hz), 10.32 ($H_C$, d, $J$ = 7 Hz)).

After a number of attempts to effect base-catalyzed closure of **6**, it was eventually found that catalytic (0.3 equiv, 0.01 M) sodium ethoxide in ethanol (5 min, 0 °C) led, with considerable stereospecificity, to methyl gibberellate. The latter predominated over its $C_3$ epimer[5b,8] (total isolated yield, 70%) by ~3:1.

Methyl gibberellate (**4**, R = $CH_3$), identical (mixture melting pointing, spectra) with the natural substance, readily crystallized from the mixture. Alternatively, the mixture could be easily oxidized to the unsaturated ketone **7** in ~70% overall yield from the aldehyde **6**, with $MnO_2$[9] in methylene chloride.[10]

It may be that the remarkable effect of the change from hydroxide in water to ethoxide in ethanol in suppressing the isogibberellic acid rearrangement is due to the fact that, in spite of appearances, the entity which undergoes rearrangement is actually the hydroxy acid salt (from lactone opening). It also

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